198 | Serum Inorganic Phosphorus

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Definition

Phosphorus is an abundant element that is widespread in its distribution. It is a major intracellular anion in mammals. Total body phosphorus in a 70-kg man is about 700 to 800 mg, 85% of which is in the skeleton in hydroxyapatite phase; the remaining 15% is in soft tissues. Almost all of the phosphorus found in the extracellular fluid space is in the form of inorganic phosphate. Serum inorganic phosphate reflects only a very minor percentage of total body phosphorus; however, it is easily measurable and gives a clue to the status of body phosphorus stores. The majority of the phosphate in the body is in the organic form as a complex with carbohydrates, lipids, and proteins. Phosphorus is an essential element in the cellular structure, cytoplasm, and mitochondrium. It is necessary for several enzymatic processes in glycolysis, ammoniagenesis as well as in oxidative phosphorylation, resulting in energy from the formation of adenosine triphosphate from adenosine diphosphate. In addition, it influences oxygen-carrying capacity of hemoglobin by its role in the regulation of 2, 3-diphosphoglycerate (2,3-DPG) synthesis.

The normal serum phosphorus concentration is 3.4 to 4.5 mg/dl (1.12 to 1.45 mmol/L). This fluctuates with age (it is higher in children than adults), dietary intake, and acid–base status. There is a diurnal variation, which reaches its nadir between 8 and 11 A.M.

The concentration of serum phosphate is generally expressed in milligrams per deciliter because concentration in millimoles can vary with acid–base status. In serum, phosphate exists in two forms, dihydrogen phosphate (H_2PO_4) and its salt, mono-hydrogen phosphate (HPO_4). The relationship between these two can be determined by the Henderson-Hasselbalch equation. At the physiologic pH of 7.40, the pK of H_2PO_4 is 6.8 and the ratio of HPO_4 to H_2PO_4 is 4 : 1. The valence of phosphorus at a pH of 7.40 is 1.8. Serum levels expressed in milligrams can be converted to millimoles per liter by multiplying by 0.323. To convert to milliequivalents, multiply the concentration in millimoles by the valence (1.8 at pH of 7.40).

About 85 to 90% of serum phosphate is free and is ultrafiltrable; 10 to 15% is bound with protein.

Technique

Serum inorganic phosphate is measured either colorimetrically or isotopically (^{32}P); the latter is not in routine use. The usual colorimetric technique is that of Fiske and Subbarow, or its modification. The principle behind the colorimetric method is the formation of phosphomolybdic acid, which is then reduced to molybdenum blue by an agent such as stannous chloride. Molybdenum blue absorbs at 660 nm. The automated method is generally offered as a part of a package with several other chemistries. In occasional cases, the determination may be interfered with by proteins, bilirubin, or organic phosphates, but these conditions are rare.

Serum phosphate should ideally be determined in the fasting state. A recent meal, high glucose ingestion, insulin release or administration, muscular activity, and hyperventilation can all lower serum phosphate by causing a shift from the plasma into the cells.

Basic Science

Phosphorus is present in ample amounts in many foods (e..g., red meat, dairy products, legumes). An average diet contains about 1.0 to 1.5 g a day. The gastrointestinal (GI) tract absorbs 75 to 80% of the ingested phosphate, and the rest is excreted in the feces. Higher phosphate intakes lead to high absorption, but the percentage of GI absorption is about the same. Low phosphate intake results in more complete absorption. Phosphate absorption is most likely via passive diffusion between cells through paracellular pathways. There is also an active transport that may be carrier mediated. At physiologic pH, phosphate uptake by luminal cells may be dependent on intraluminal sodium. Phosphate is absorbed throughout the entire intestine, but the major site is the jejunum, followed by the duodenum and ileum. Jejunal absorption is vitamin D dependent. The major route of excretion is by the kidneys. About 80% of the plasma protein is ultrafiltrable. Under usual conditions, about 85 to 90% of filtered phosphorus is reabsorbed. The reabsorption of phosphate is passive, occurring primarily in the proximal tubules. The reabsorption of phosphate by proximal tubules is not homogeneous. A large component of filtered phosphate is reabsorbed in the early portions of the tubules, and the rest by the remaining part of the proximal tubule. Beyond the proximal tubule, the mode and sites of phosphate reabsorption are controversial, but it appears that phosphate transport probably occurs in the pars recta as well as the early and late distal tubules. Micropuncture studies virtually exclude the loop of Henle as a site of transport. Phosphate reabsorption in the proximal tubule appears to be closely linked to sodium transport, but is independent of sodium in response to glucose load and insulin administration.

Several factors modify the reabsorption of phosphate and can be classified as hormonal and nonhormonal (Table 198.1). Tubular reabsorption of phosphate has a maximum, the T_m, which will be altered by many of the factors described in Table 198.1. The tubular reabsorption of phosphorus has been used as a clinical test for parathyroid activity.

Disorders of serum phosphorus may occur from three possible mechanisms: dietary intake, GI disorders, and renal handling. Phosphorus is abundant in the diet; therefore, dietary deficiency of phosphate is unlikely, although it can occur in prolonged starvation or with certain GI disorders

Table 198.1
Factors Affecting the Tubular Reabsorption of Phosphate

Increased reabsorption	Decreased reabsorption
Hormonal	*Hormonal*
Insulin	Parathyroid hormone
Growth hormone	Calcitonin
Vitamin D or its metabolite (acute administration)	Glucocorticoids
	Thyroid
Nonhormonal	*Nonhormonal*
Hypercalcemia	Extracellular volume expansion
Hypermagnesemia	Diuretics
Dietary restriction of phosphate intake	Alcohol ingestion
	High dietary intake
	Urinary alkalinization

such as intractable vomiting, malabsorptive states, and acute diarrheas. The kidney remains the most significant organ regulating phosphate homeostasis, and most of the clinical perturbations seen are caused by renal phosphate wasting.

Phosphorus forms cell membranes and participates in the activity of mitochondria, DNA, RNA, and various nucleotides. It regulates oxygen-carrying capacity by its role in regulating the level of 2,3-DPG, and takes part in enzymatic reactions involving glycolysis, ammoniagenesis, and 1,25-hydroxyvitamin D_3 hydroxylase. Deficiency of phosphate therefore has far-ranging effects and affects virtually every part of the body. The consequences of phosphate deficiency are summarized in Table 198.2. Most of the adverse effects occur only with marked phosphate depletion. Mild to moderate phosphate deficiency is generally well tolerated (serum phosphorus levels between 1 and 3.5 mg/dl), but phosphorus is an integral part of the cell's energy production and any phosphate deficiency can affect vital cellular functions. The symptoms of phosphate deficiency generally occur with serum phosphate levels below 1 mg/dl. In general, patients become anorectic, weak, and may complain of bone pain. Abnormalities of red blood cells include a decrease in 2,3-DPG and adenosine triphosphate, resulting in depression of P_{50} values with a decreased release of oxygen to peripheral tissue. Hemolytic anemia may also develop in severe deficiency states. Leukocyte functions such as chemotaxis and phagocytosis may also be impaired. Severe phosphate deficiency might also produce severe reversible cardiomyopathy. In the presence of phosphate deficiency, an impairment of bone mineralization leads to widening of the osteoid seam. Mental confusion is a recognized complication of severe phosphate depletion and may result from a decrease in 2,3-DPG, interfering with oxygen release. A characteristic of severe hypophosphatemia is skeletal muscle damage with an elevation of the serum creatine phosphokinase and aldolase levels, and in some cases rhabdomyolysis. Pulmonary muscle weakness may result from hypophosphatemia and, in some cases, may impede weaning from a ventilator. Hypophosphatemia causes decreased absorption of calcium in the renal tubules, leading to hypercalciuria. In addition, hypophosphatemia alters renal acid–base status by four possible mechanisms: depressed proximal tubular reabsorption of bicarbonate, leading to bicarbonate wasting; impaired distal tubular acidification; decreased buffer excretion due to low phosphate excretion; and diminished renal ammoniagenesis.

Table 198.2
Clinical and Biochemical Manifestations of Marked Hypophosphatemia

Hematologic alterations
- Red blood cells
  - Decreased ATP
  - Decreased 2,3-DPG
  - Decreased P_{50}
  - Increased oxygen affinity
  - Decreased lifespan
  - Hemolysis
  - Spherocytosis
- Leukocytes
  - Decreased phagocytosis
  - Decreased chemotaxis
  - Decreased bactericidal activity
- Platelets
  - Impaired clot retraction
  - Thrombocytopenia
  - Decreased ATP
  - Megakaryocytosis
  - Decreased lifespan

Skeletal abnormalities
- Bone pain
- Radiolucent areas (x-ray)
- Pseudofractures
- Rickets or osteomalacia

Central nervous system
- Anorexia
- Irritability
- Confusion
- Paresthesias
- Dysarthria
- Coma

Cardiovascular
- Decreased cardiac output
- Increased left ventricular end-diastolic pressure

Muscular
- Muscle weakness
- Rhabdomyolysis
- Decreased transmembrane resting potential

Biochemical
- Low PTH levels
- Increased 1,25-$(OH)_2D_3$
- Hypercalcemia
- Hypomagnesemia
- Hypermagnesuria
- Hypophosphaturia
- Decreased GFR
- Decreased T_m for bicarbonate
- Decreased renal gluconeogenesis
- Decreased titrable acid excretion
- Increased creatine phosphokinase
- Increased aldolase

Source: Reproduced with permission from Slatopolsky E. Pathophysiology of calcium, magnesium, and phosphate metabolism. In: Klahr S, ed. The kidney and body fluids in health and disease. New York: Plenum, 1983.

Clinical Significance

Disorders of phosphate homeostasis occur in a wide range of clinical conditions. Both hyper- and hypophosphatemia can be caused by cellular shifts of phosphate. The three primary conditions that lead to phosphate dysfunction are dietary intake, GI, and renal status. Since serum inorganic phosphate is only a minute portion of body phosphate, al-

terations in the serum level can occur when the body phosphate is low, normal, or high.

Hyperphosphatemia

The common causes of hyperphosphatemia are summarized in Table 198.3. Apart from cellular shifts, most hyperphosphatemia occurs in the presence of renal insufficiency with a decrease in phosphate excretion. In chronic renal failure, significant hyperphosphatemia is not seen until the GFR has fallen below 25 ml/min, although early phosphate retention causes a decrease in ionized calcium, leading to increased parathyroid hormone and initiation of a whole cascade of events that ultimately produce renal osteodystrophy.

Hyperphosphatemia occurs in several endocrine conditions associated with increased tubular reabsorption of phosphate. In pseudohypoparathyroidism, there is failure of parathyroid hormone to act on renal tubules, resulting in a high T^m which is responsible for the high serum phosphate in the presence of an abnormal circulating parathyroid hormone. In acromegaly, excess growth hormone leads to increased tubular reabsorption of phosphate. In other clinical situations with a high serum phosphate, there is increased tubular reabsorption of phosphate. Thus, in magnesium deficiency there is decreased release of parathyroid hormone, producing a picture similar to hypoparathyroidism. In tumoral calcinosis, a condition seen more frequently in blacks, there appears to be primary increased tubular reabsorption of phosphate with normal GI absorption of calcium. With the administration of vitamin D or its analogs, there is increased absorption of calcium and phosphate from the gastrointestinal tract; if there is some degree of renal insufficiency, hyperphosphatemia may result.

Table 198.3
Causes of Hyperphosphatemia

Cellular shift (from cells to ECV)
Neoplastic: leukemias, lymphomas
Increased catabolism, e.g., rhabdomyolysis
Respiratory acidosis, diabetic ketoacidosis, tissue ischemia
Decreased renal excretion
Renal failure, acute and chronic
Hypoparathyroidism
Pseudohypoparathyroidism, Type I and II
Abnormal circulating parathyroid hormone
Other endocrine disorders, hyperthyroidism, acromegaly, juvenile hypogonadism
Increased phosphate load
Oral loads: vitamin D intoxication, phosphate-containing laxatives, high dietary phosphate (in presence of decreased GFR)
Parenteral: intravenous phosphorus, transfusion of old blood (hemolysis)
Miscellaneous
Cortical hyperosteosis
Volume contraction
Familial intermittent hyperphosphatemia
Magnesium deficiency (impaired PTH secretion)
Tumoral calcinosis

Source: Adapted with permission from Slatopolsky E. Pathology of calcium, magnesium, and phosphate metabolism. In: Klahr S, ed. The kidney and body fluids in health and disease. New York: Plenum, 1983.

The symptomatology of hyperphosphatemia is related to the conditions producing it. The most common risk is ectopic or metastatic calcification, which may occur if the product of the serum calcium and phosphorus exceeds 70. The calcification may occur in any organ, although it is seen most commonly in the cornea, conjunctiva, lungs, and skin. The calcification is facilitated by alkalosis. Vascular calcification can produce gangrene as well as deposits in the cardiac conducting system. Therapy consists of identifying the underlying cause and correcting it. In renal insufficiency, therapy consists of controlling dietary intake of phosphates and use of phosphate binders. Initiation of dialysis helps in controlling serum phosphate levels, but in itself is rarely effective.

Hypophosphatemia

Hypophosphatemia usually implies a serum concentration of less than 2.5 mg/dl. However, phosphate levels below 1 mg/dl are commonly symptomatic, and such levels are often labeled as severe hypophosphatemia. Phosphorus depletion is characterized by reduction in total body phosphorus stores. However, hypophosphatemia (mild, moderate, or severe) can occur without phosphate depletion. The common causes of hypophosphatemia are listed in Table 198.4.

Hypophosphatemia is seen most frequently in hospitalized patients. The three primary mechanisms leading to hypophosphatemia are: (1) transcellular shift of phosphorus (from extracellular volume to either soft tissues or bones); (2) poor dietary intake, especially when associated with impaired GI absorption or diarrhea; and (3) increased phosphate excretion resulting from renal and nonrenal causes. The nonrenal loss occurs through the gut, primarily malabsorptive states or diarrheal conditions. A simple deficiency of vitamin D will lead to rickets in childhood and osteomalacia in adults, along with poor phosphate absorption. Phosphate binders, such as nonabsorbable antacids containing aluminum, bind phosphorus in the gut and block the absorption of both ingested and secreted phosphate.

Major losses of phosphorus can occur through the kidneys. The usual cause of renal phosphate wasting is excess parathyroid hormone, which reduces the maximum renal tubular reabsorption of phosphorus. These defects may be congenital or acquired. Among the congenital defects, the best known is Fanconi's syndrome—a proximal tubular disorder producing phosphaturia, glycosuria, aminoaciduria, uricosuria, and bicarbonaturia. A similar picture may also be seen in cystinosis, Wilson's disease, hereditary fructose intolerance, and glycogen storage disease. Acquired defects include multiple myeloma, amyloidosis, and heavy metal intoxication. In postrenal transplantation, a state of secondary hyperparathyroidism may exist, with high circulating parathyroid hormone resulting in phosphate wasting by normal renal tubules. Such a state may persist for several months. Vitamin D-resistant rickets is believed to be caused by a phosphate leak from renal tubules along with defective intestinal absorption of phosphate.

Renal tubular wasting can also occur during extracellular volume expansion with saline or bicarbonate. Such a picture can be seen during the diuretic phase of acute tubular necrosis or with the use of diuretic agents.

In several clinical settings, hypophosphatemia may be the result of a combination of factors. In diabetic ketoaci-

Table 198.4
Causes of Hypophosphatemia

Cellular shift (from ECV to soft tissues and bone)
- Glucose ingestion or IV infusion
- High carbohydrate diet
- Fructose or glycerol administration
- Insulin administration
- Total parenteral nutrition (hyperalimentation)
- Gram-negative bacteremia secondary to hyperventilation
- Salicylate poisoning secondary to hyperventilation
- Respiratory alkalosis

GI
- Poor dietary intake
- Starvation and malnutrition
- Malabsorption
- Vitamin D deficiency
- Phosphate binders

Renal loss
- Primary hyperparathyroidism
- Secondary hyperparathyroidism with normal renal function
- ECV expansion
- Sodium bicarbonate infusion
- Diuretic therapy
- Renal tubular defects (acquired and congenital)
- Post renal transplantation (persistant secondary hyperparathyroidism)
- Hypokalemia
- Hypomagnesemia

Abnormalities in vitamin D metabolism
- Vitamin D-deficient rickets
- Vitamin D-resistant rickets
- Vitamin D-dependent rickets

Miscellaneous
- Alcoholism
- Alcohol withdrawal
- Pharmacologic phosphate binders
- Severe burns
- Nutritional recovery syndromes
- Severe respiratory alkalosis

Source: Adapted with permission from Slatopolsky E, Pathology of calcium, magnesium, and phosphate metabolism. In: Klahr S, ed., The kidney and body fluids in health and disease. New York: Plenum, 1983.

dosis, initially there is a higher serum phosphate due to the acidosis. With treatment, there is increased urinary excretion along with translocation of phosphate into cells during the administration of insulin and glucose. Hypophosphatemia may be seen in 50% of patients hospitalized with chronic alcoholism. Mechanisms include poor dietary intake, vomiting, diarrhea as well as magnesium deficiency, ketoacidosis, and an effect of ethanol per se. Alcoholic ketoacidosis probably produces decomposition of intracellular organic phosphate with the release of phosphate, leading to phosphaturia. In severe burns, hypophosphatemia is usually seen from the second to the fifth day after the injury and may persist up to ten days. The mechanism for hypophosphatemia is not known, but may include respiratory alkalosis resulting from gram-negative sepsis, renal phosphate wasting secondary to volume expansion, and in-

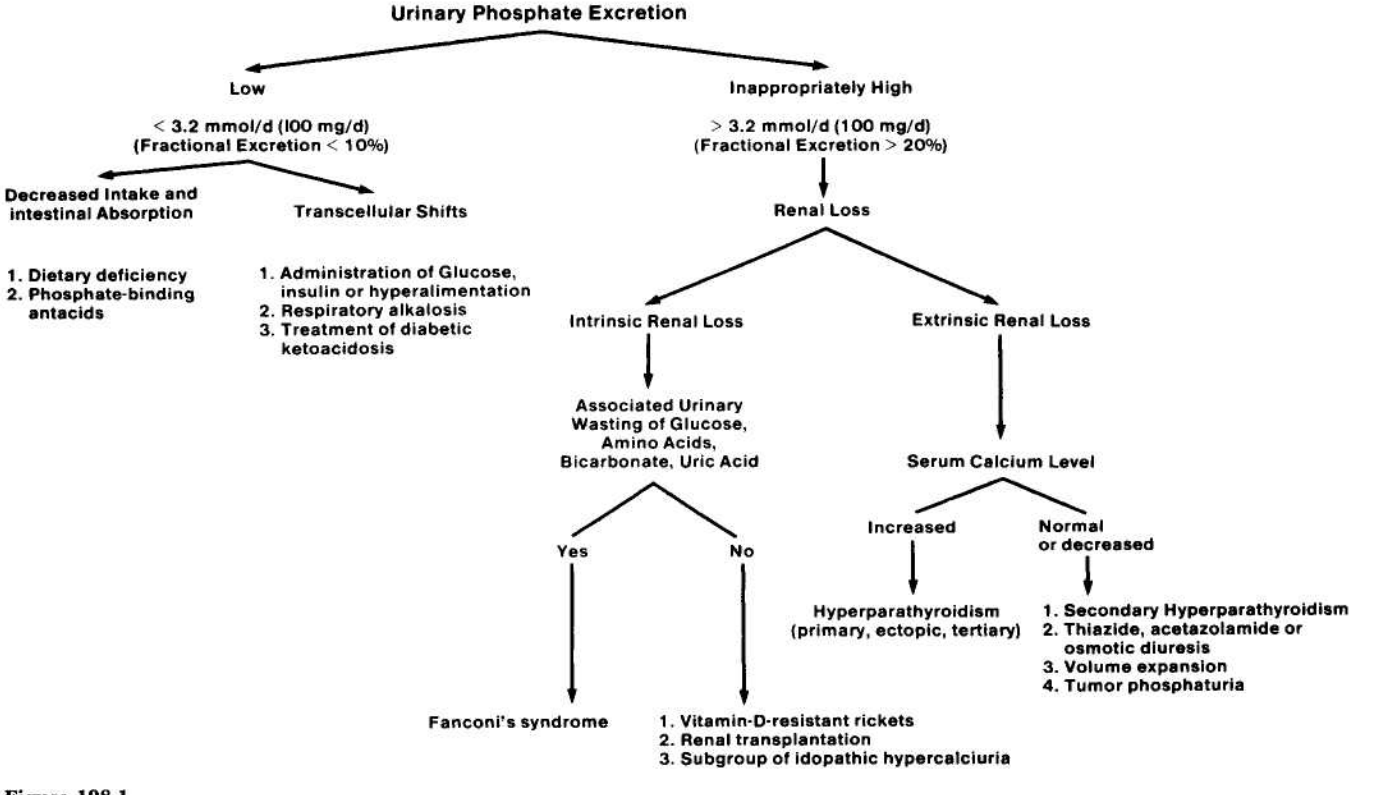

Figure 198.1
Clinical approach to hypophosphatemia. (Reproduced with permission from Berkelhammer CA, Bear RA. A clinical approach to common electrolyte problems: 3. Hypophosphatemia. Can Med Assoc J 1984;130:17–23.)

creased calcitonin and catecholamine levels. Similarly, in patients recovering from starvation (nutritional recovery) or maintained on intravenous nutrition, especially if without phosphates, anabolism leads to cellular uptake of phosphate. At times, there may be marked symptomatic hypophosphatemia.

Urinary phosphate determination can be a valuable guide in the diagnosis of hypophosphatemia. Kidneys avidly conserve phosphate when hypophosphatemia is present and may produce virtually a phosphate-free urine. Thus, when the serum level of phosphate is very low (1.5 mg/dl or 0.48 mmol/L), increased urinary phosphorus excretion (higher than 3.2 mmol/dl or fractional excretion of 20%) is inappropriate and clearly indicates renal wasting. In contrast, if urinary phosphate is low in the setting of low serum phosphate (i.e., if the urinary phosphate excretion is less than 3.2 mmol/day or the fractional excretion is less than 10%) then nonrenal causes should be investigated. The approach is summarized in Figure 198.1.

The therapy of hypophosphatemia involves recognizing the cause and correcting the underlying condition. Phosphate supplementation is not required for mild to moderate asymptomatic hypophosphatemia. But severe hypophosphatemia (less than 1.0 mg/dl) or symptomatic hypophosphatemia requires prompt correction. Phosphate can be replaced by either oral or parenteral administration. Like potassium, phosphate replacement therapy is empiric because total body phosphorus is not determined easily. Periodic checking of the serum phosphate is required during replacement therapy.

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